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Update on Essential Tremor and Huntington's Disease Behavioral and Cognitive Comorbidities

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Disclosures

- No relevant financial relationships with commercial interests
- Dr. Pontone has consulted for AbbVie and Cognition Therapeutics
- The following talk may include unlabeled/unapproved use of medications

Neuropsychiatric and Cognitive Symptoms in Essential Tremor

Prevalence, mechanisms, and evidence-based management



November 2026

ET is more than a tremor

~7 million

people with ET in the US (>2% of the population)

2×

mortality rate once dementia develops in ET, with loss of functional ability

Cognitive

A full spectrum from mild difficulty to frank dementia, likely neurodegenerative

Psychiatric

Depression, anxiety, social phobia, apathy and personality changes

Sensory

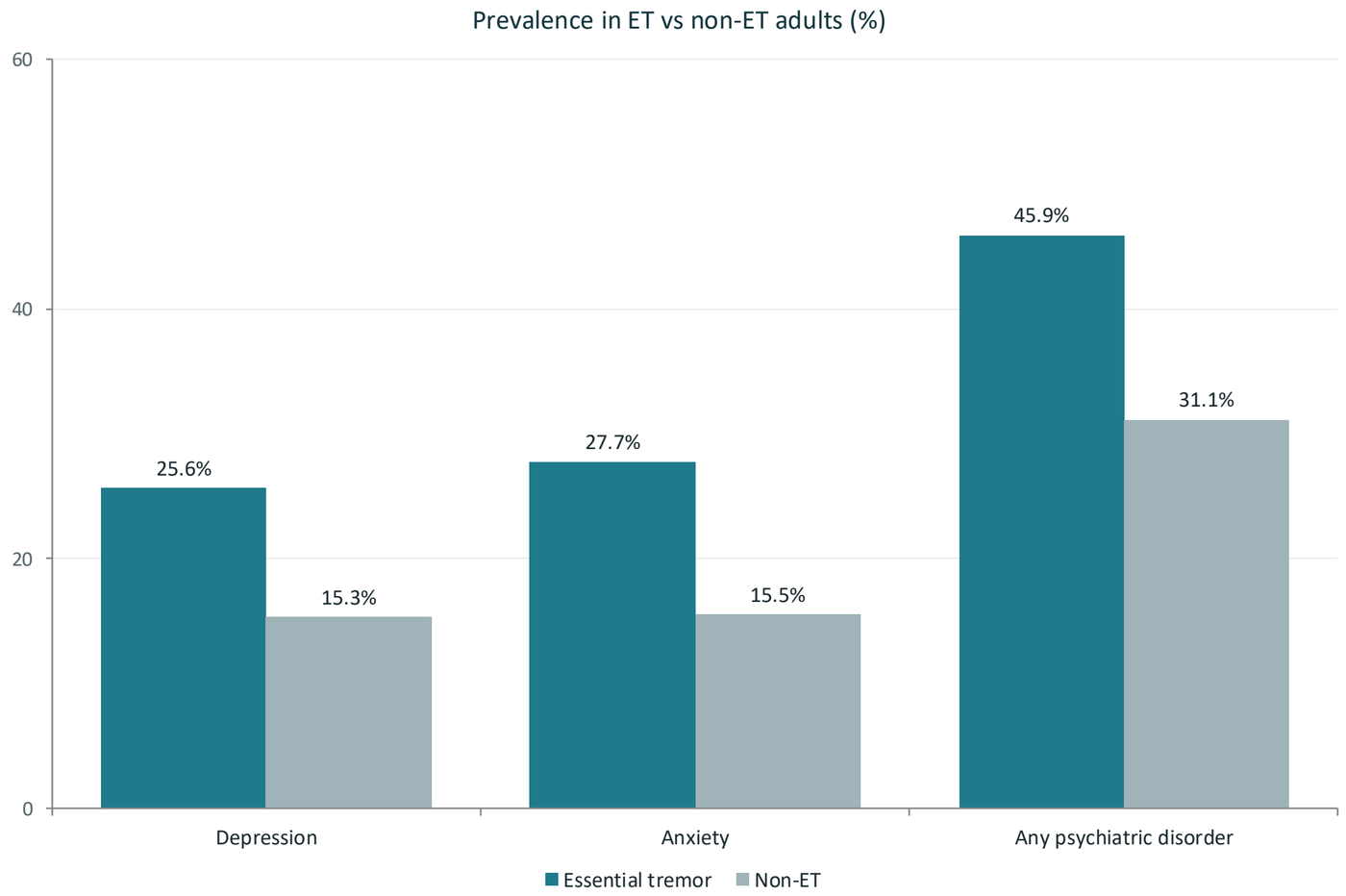
Hearing impairment and possibly olfactory deficits

Sleep & function

Poor sleep quality, balance problems and increased fall risk

Sources: Louis 2015 (non-motor domains); Gerbasi 2022 (SLR); Ghanem/Louis, AAN 2024 abstract (mortality); MIMS report of AAN 2024 (US prevalence).

Depression and anxiety are more common in ET



0.55

SMD in depression/anxiety scale scores, ET vs non-ET (95% CI 0.22 to 0.87; meta-analysis)

63%

had at least mild anxiety; 54% at least mild depression (clinic cohort, n=245)

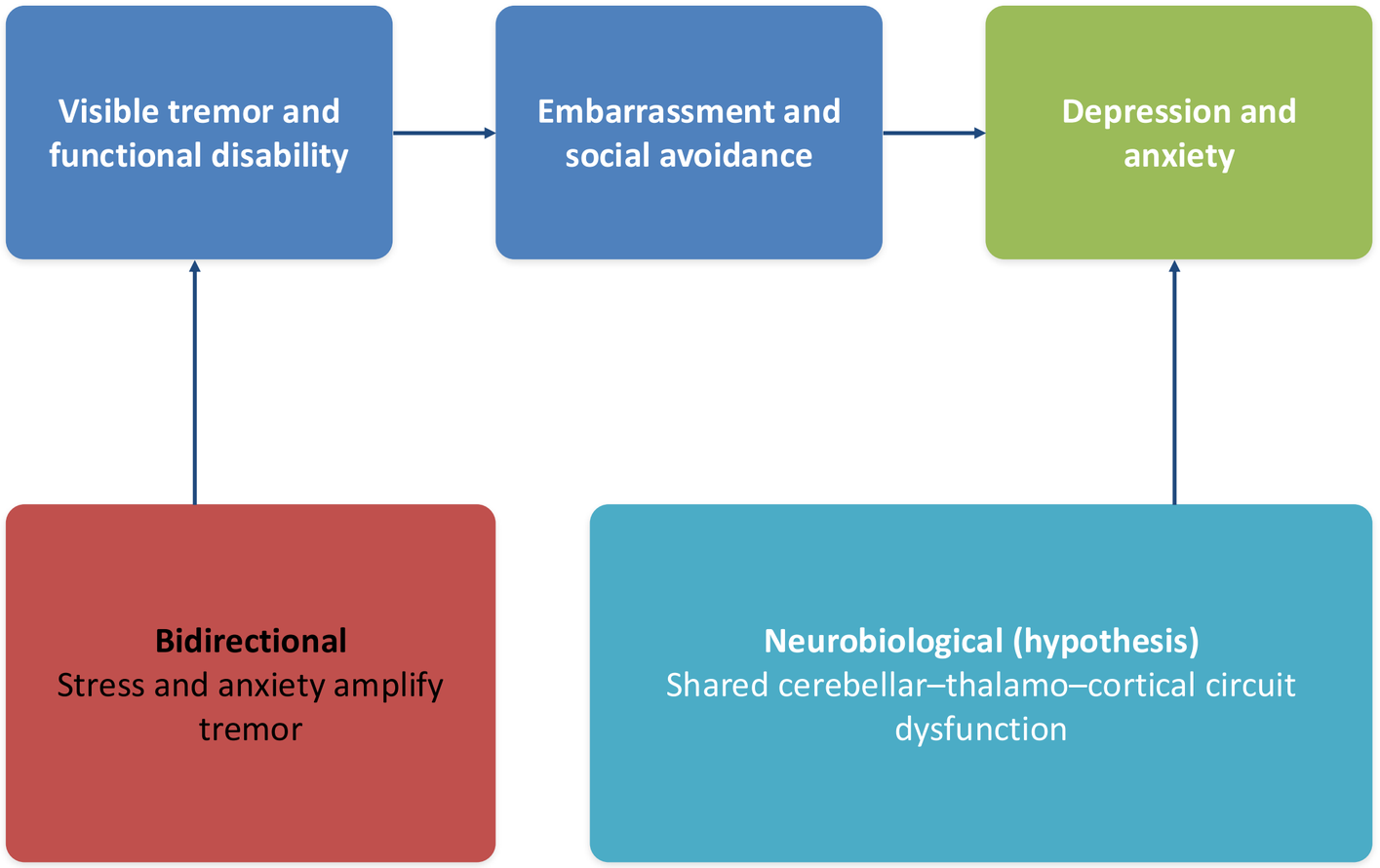
5–48%

moderate to severe depression across studies (anxiety 14–71%): wide variability

Chart: US claims analysis (aOR depression 1.56, anxiety 1.78), sponsor-presented AAN 2022 abstract. Meta-analysis: Shang 2022. Cohort: Huang 2019.

Mood symptoms: reaction, biology, or both?

Psychosocial pathway



What the data show

- Risk factors: female sex, cranial tremor, greater functional disability
- No correlation with clinician-rated arm or leg tremor severity
- Several studies suggest symptoms are not simply a reaction to disability
- Worse anxiety and depression track with lower MMSE scores

Sources: Huang 2019 (n=245); Louis 2015; J Neural Transm 2025 (cites Lenka 2017, Bologna 2019). Circuit model is a hypothesis, not established causation.

Cognitive profile: what is affected?

Domains most often affected

Attention

Sustained focus and processing

Executive function

Planning, flexibility, verbal fluency

Memory

Learning and delayed recall

−1.16

SMD on MMSE, ET vs non-ET (95% CI −1.75 to −0.58)

NS

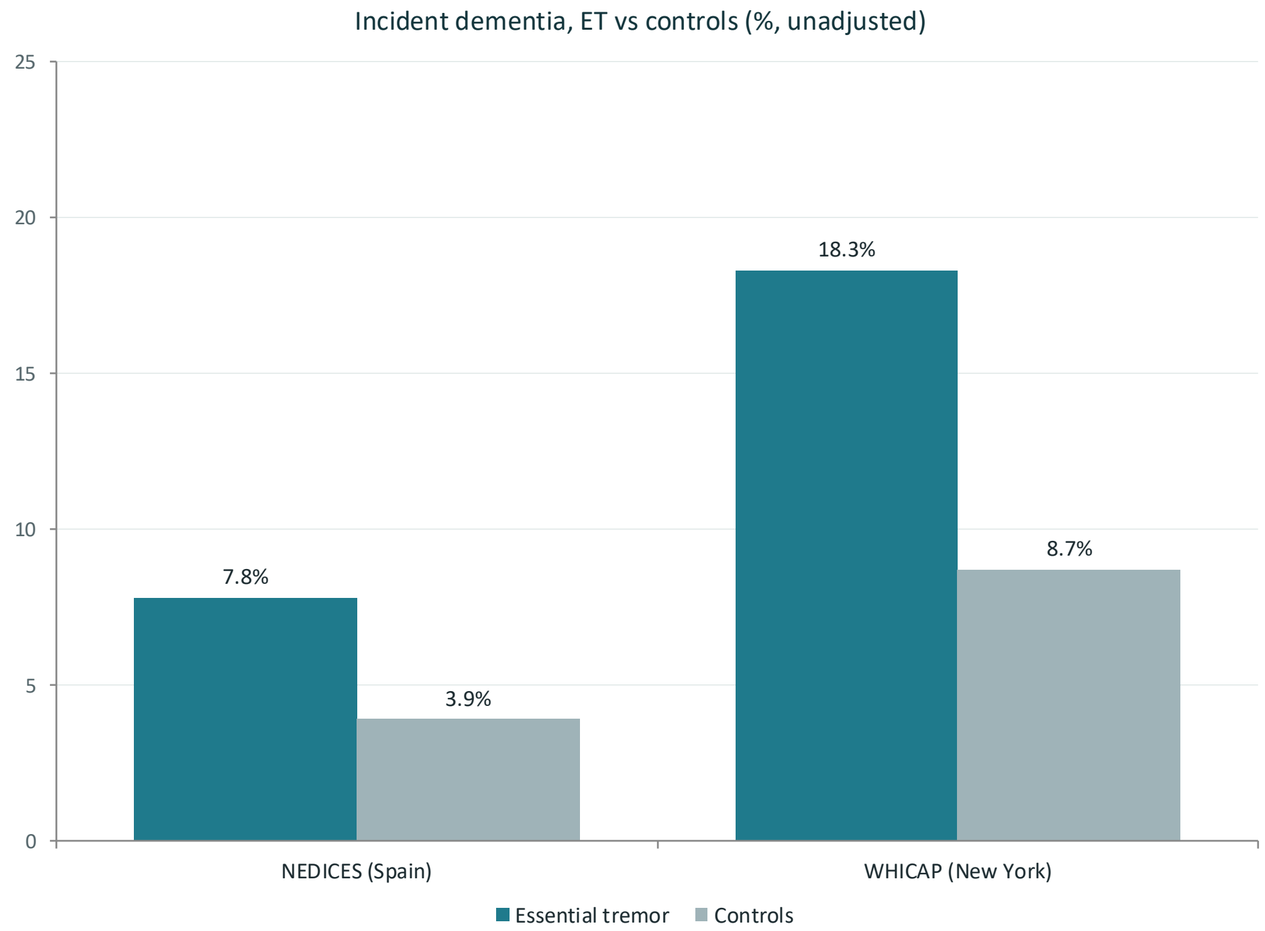
No significant MoCA difference between groups: results differ by screening tool

2.49

Odds ratio for dementia and affective disorders combined (95% CI 2.17–2.85)

Shang 2022 meta-analysis of observational studies (causal relationship unclear); Thawani 2009 (frontal-executive and memory deficits).

Dementia risk: elevated, but findings vary



Adjusted estimates cross 1.0: NEDICES RR 1.66 (0.99–2.80); WHICAP HR 1.64 (0.99–2.72)

Elderly-onset ET (>65 y): RR 1.98 (1.14–3.45); no excess with earlier onset

Prospective ET cohort (2024): MCI 26.6% (14.5% general population), dementia 18.5%, MCI to dementia 12.2%/year

Mayo 10-year cohort: no excess dementia risk; baseline MCI strongest predictor (HR 6.98)

Bermejo-Pareja 2007 (3.2-y follow-up); Thawani 2009; Ghanem/Louis and Sherfinski, AAN 2024 abstracts. Designs and follow-up differ; not directly comparable.

Assessment: screen mood and cognition

Domain	Practical tools	Who to prioritize and what to do
Depression	PHQ-9, HADS-D, or GDS in older adults	Women, cranial tremor, high disability. Ask about safety if positive
Anxiety, incl. social	GAD-7 or HADS-A; ask about avoidance	Avoidance of eating, writing, public situations; consider CBT
Cognition	MoCA or MMSE plus informant history	Onset after 65, subjective decline, MCI. Abnormal: neuropsychological testing
Contributors	Medication, alcohol, sleep, B12/thyroid review	Reduce primidone, topiramate, benzodiazepines where mood or cognition suffers

Screening is supported by authors of observational cohorts; tools listed are practical suggestions (expert opinion), not an ET-validated algorithm.

Huang 2019 (screen women, cranial tremor, disability); Thawani 2009 (routine dementia assessment); Alberta Health Services ET pathway (alcohol and medication review).

Tremor drugs: efficacy vs brain safety

Agent	MDS-EBM rating	Neuropsychiatric considerations
Propranolol	**Clinically useful**	Fatigue, hypotension, bradycardia. Depression reported: caution if active depression
Primidone	**Clinically useful**	Sedation, first-dose reactions; depression, cognitive and behavioral effects. Poorly tolerated in older adults
Topiramate (>200 mg/day)	**Clinically useful**	Cognitive slowing, concentration difficulty; more dropouts than placebo (risk difference 19%). Avoid in cognitive impairment
Alprazolam	**Possibly useful**	Sedation, cognitive effects, dependence: limit use, especially in older adults
Botulinum toxin A	**Possibly useful**	Local injection; dose-dependent, transient hand weakness

Ratings (limb tremor): Ferreira 2019, MDS Evidence-Based Medicine review (64 studies). Adverse effects: BMJ Clinical Evidence; topiramate RCT meta-analysis; Tremor J primidone review; Alberta pathway.

Procedures: cognitive and mood outcomes

Deep brain stimulation (VIM, cZi/PSA)

MDS-EBM: possibly useful

- 20 studies (13 prospective): significant cognitive decline appears rare
- Left VIM DBS: some patients worse on verbal abstraction, word recall, verbal memory

MR-guided focused ultrasound (unilateral)

MDS-EBM: possibly useful

- Two cohorts (n=33 and n=22): no group-level cognitive decline
- Practice point: screen cognition and mood before any procedure

MRgFUS at 1 year

Hamilton Anxiety scale

5.7 → 2.7

ET quality of life (QUEST)

35.0 → 9.0

Both changes p<0.001; mood also improved. Open-label cohort that included Parkinson tremor.

Ferreira 2019 (ratings); Al Ali 2024 (DBS review); Rohringer 2024; Saporito 2024 (COGNIFUS part 2). Lower scores = better on both scales.

Managing depression and anxiety in ET

Evidence gap: this review found no ET-specific trials of psychotherapy or antidepressants; advice is extrapolated from general psychiatry.

Psychotherapy (CBT)

Most effective treatment for social anxiety; also targets avoidance and low mood

Medication

Follow standard guidelines; monitor tremor after starting, as some agents can worsen it

Control the tremor

Effective tremor treatment may ease mood and anxiety (observational MRgFUS data)

Function and stigma

Occupational therapy, adaptive tools, peer support such as the IETF

Alcohol

Ask about alcohol used to calm tremor; screen for dependence

Safety and referral

Assess suicidality if depressed; refer moderate, severe or refractory cases

Sources: IETF resource on ET, depression and anxiety; Alberta Health Services ET pathway; Saporito 2024. Antidepressant tremor effects are a general pharmacological caution.

A practical care pathway

1 Screen

- Mood and anxiety (PHQ-9/GAD-7 or HADS)
- Cognition (MoCA/MMSE) plus informant
- Prioritize women, cranial tremor, disability, onset after 65
- Repeat periodically

2 Choose tremor therapy

- Propranolol first unless active depression
- Primidone or topiramate: caution with low mood or cognitive impairment
- Limit benzodiazepines
- Refractory: MRgFUS or DBS after cognitive screen

3 Treat comorbidity

- CBT with or without medication
- Cognitive impairment: reversible causes, deprescribe CNS-active drugs
- Refer: psychiatry, neuropsychology, memory clinic

4 Reassess

- Re-screen 8–12 weeks after any therapy change
- Track tremor, mood, cognition, function
- Revisit plan with decline or intolerance

Synthesis of MDS-EBM 2019, cohort data and clinical pathways; practice suggestions, not a formal guideline.

Key takeaways

1. Depression, anxiety and cognitive problems are common in ET: screen routinely
2. Mood symptoms track cranial tremor and disability, not arm tremor severity
3. MCI is about 2× and dementia up to about 3× general rates in some cohorts, but results are mixed
4. Choose tremor treatment with the brain in mind: caution with primidone, topiramate and benzodiazepines

Research gaps

- Trials of psychotherapy and antidepressants in ET
- Causal links between ET, MCI and dementia
- Standardized cognitive batteries and biomarkers
- Long-term cognitive safety of procedures

Neuropsychiatric symptoms in Huntington’s disease

Learning objectives

- Describe the prevalence and natural history of neuropsychiatric symptoms (NPS) in HD
- Explain the cortico-striatal basis of depression, apathy, irritability and OCD
- Apply structured assessment, including suicide risk screening
- Select evidence-informed pharmacologic and non-pharmacologic treatments
- Recognise the limits of the evidence and the need for individualised care

Huntington's disease: the basics

AD

Autosomal dominant
CAG repeat in HTT

≥40

CAG repeats:
full penetrance

35–45

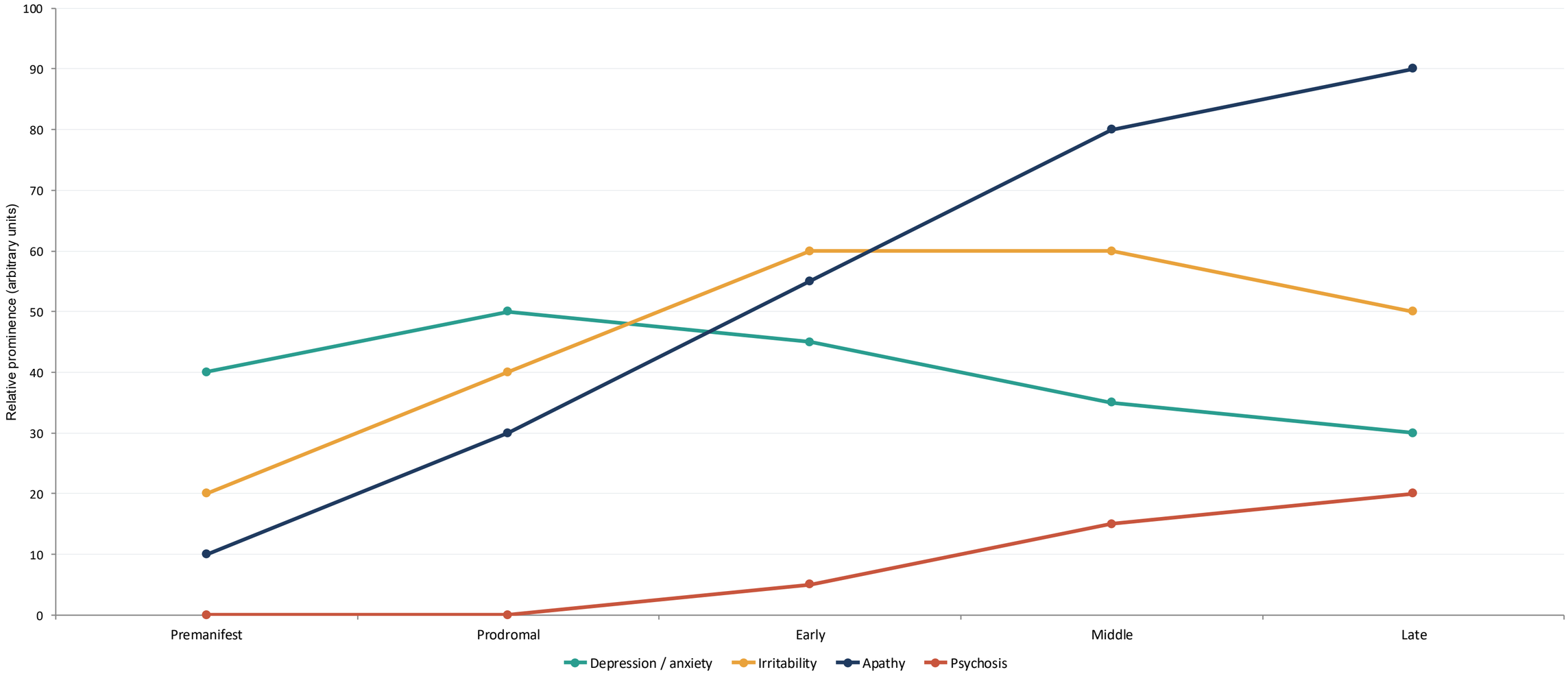
Typical age at
clinical onset (yrs)

3 domains

Motor, cognitive,
neuropsychiatric

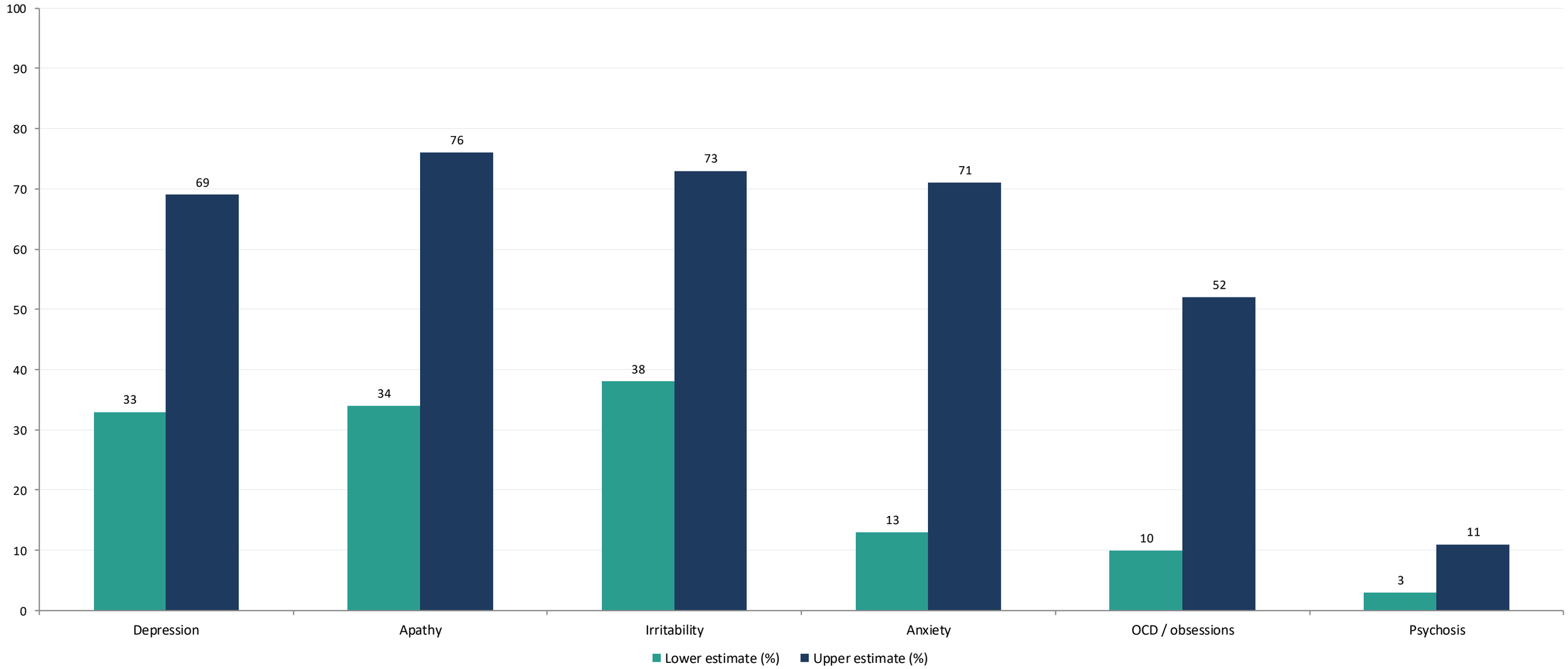
- NPS often precede motor diagnosis by years and drive disability, admission and caregiver burden
- Cognitive and psychiatric features are frequently more distressing to families than chorea

Neuropsychiatric symptoms across the disease course



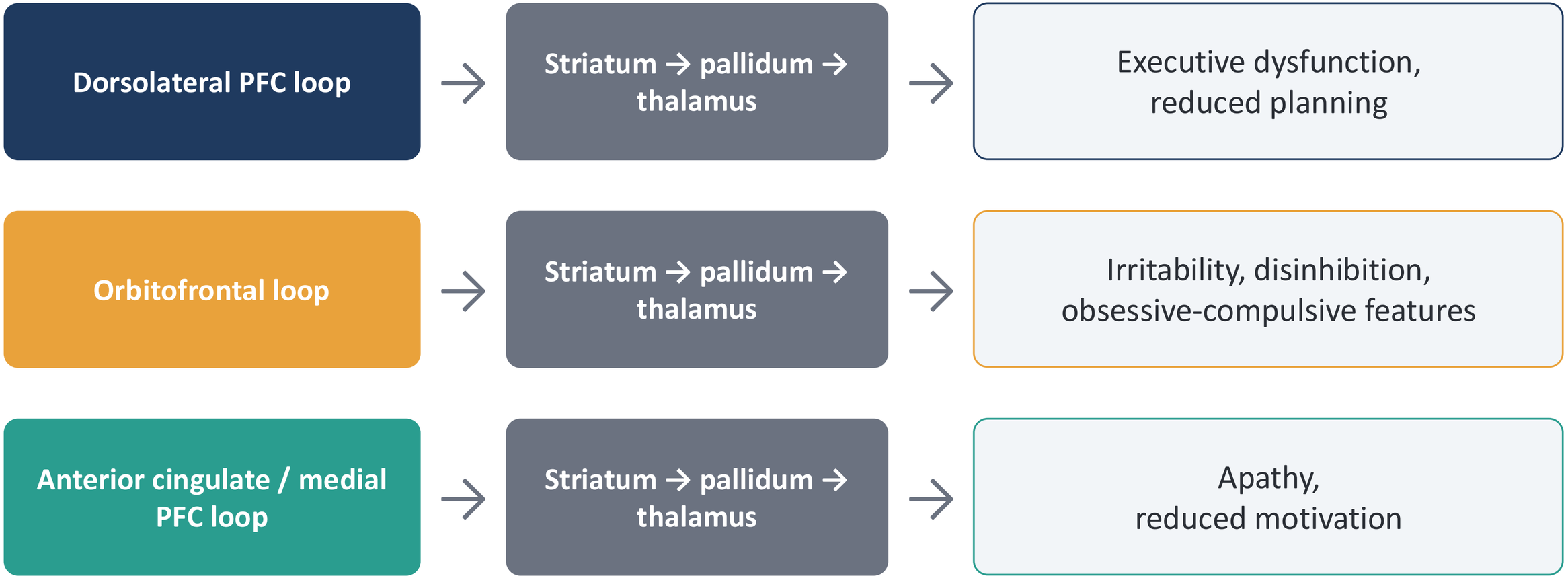
Schematic illustration of general trends only; not patient-level data. Based on Paulsen 2005; Epping 2016; Van Duijn 2014.

How common are they? Prevalence ranges



Range of reported prevalence across studies. Van Duijn et al., Mov Disord 2014 (Registry/clinic cohorts).

Neurobiology: frontostriatal circuits



Also implicated: serotonergic and dopaminergic dysregulation, HPA-axis changes, white-matter loss, inflammation

Assessment: tools and approach

Domain	Tool	Notes
Global NPS	Problem Behaviours Assessment – short (PBA-s)	Clinician-rated; severity x frequency
Depression	HADS, BDI-II, Cornell, PHQ-9	Self-report less valid as cognition declines
Apathy	Apathy Evaluation Scale (AES)	Use informant version
Irritability	Irritability Scale, Overt Aggression Scale	Assess triggers and frequency
Suicidality	C-SSRS; clinical interview	Ask at every visit, especially at transitions
Cognition	MoCA, SDMT, Stroop	Cognitive load shapes treatment choice

Always screen for: delirium, medication effects, sleep, pain, substance use, psychosocial stressors

Depression

Clinical picture

- Low mood, anhedonia, guilt, hopelessness
- Early in the disease and around diagnosis or loss of function
- Often atypical: irritability, agitation, sleep disruption
- Under-recognised; cognitive impairment masks symptoms

Treatment approach

- First line: SSRI (sertraline, citalopram, escitalopram) or mirtazapine
- Alternatives: venlafaxine, bupropion; avoid strongly anticholinergic agents
- CBT, behavioural activation; supportive therapy
- ECT for severe or refractory depression or psychotic depression
- Review VMAT2 inhibitor if started

Apathy vs depression: a key distinction

Feature	Apathy	Depression
Core change	Loss of initiation and goal-directed behaviour	Sadness, anhedonia, guilt
Emotional distress	Often absent; reduced insight	Present
Cognitive content	Few thoughts or plans	Negative thoughts, hopelessness
Suicidal ideation	Not typical	May be present
Course in HD	Increases with progression	Peaks early; fluctuates
Treatment evidence	None established; structured routines, caregiver coaching	SSRIs, mirtazapine, CBT (limited HD trials)

Irritability and aggression

Approach

- Identify triggers: pain, fatigue, noise, change of routine
- Predictable schedule; calm, concise communication
- Treat comorbid depression, anxiety, akathisia
- Safety plan for family; crisis contacts

Medication options

- SSRIs (first line)
- Atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole) if severe
- Mood stabilisers (valproate, carbamazepine, lamotrigine)
- Propranolol or buspirone in selected cases
- Evidence mainly open-label / case series

Anxiety, obsessions and compulsions

Anxiety

- Common from early stages
- Worsened by uncertainty, loss of control and change
- SSRIs or SNRIs first line; buspirone
- Short-term benzodiazepines only; fall and cognitive risk
- CBT adapted for cognition; relaxation and routine

Obsessive-compulsive features

- Perseveration vs true OCD: consider executive dysfunction
- SSRIs, often at higher OCD-range doses
- Add low-dose atypical antipsychotic if refractory
- Environmental structure and distraction strategies

Psychosis

Features

- Prevalence about 3–11%
- Delusions (jealousy, paranoia) more common than hallucinations
- Associated with family history of psychosis
- Can respond slowly; relapse common

Treatment

- Atypical antipsychotics: olanzapine, risperidone, quetiapine, aripiprazole
- Clozapine for refractory cases (monitoring required)
- Low dose, titrate slowly; monitor for parkinsonism, dysphagia, metabolic effects
- ECT if resistant

Suicide risk

≈4–8×

higher suicide rate than the general population (estimates vary)

~20%

report suicidal ideation at some point

~10%

report a lifetime suicide attempt

- High-risk periods: pre-diagnosis, early stage, loss of independence, bereavement
- Ask directly at every visit; use C-SSRS; involve family
- Limit access to lethal means; collaborative safety plan
- Treat depression, impulsivity, substance use; consider lithium or clozapine only with specialist guidance

Approximate figures from the literature (e.g., Paulsen 2005; Hubers 2012); verify current estimates before citing. Crisis line (US): 988.

Treatment principles

1	**Assess and exclude**	Medical, medication, sleep, pain, substance causes
2	**Non-drug first**	Structure, routine, caregiver education
3	**Target the main symptom**	One drug at a time; start low, go slow
4	**Minimise harm**	Falls, dysphagia, sedation, cognition
5	**Review often**	Stop ineffective drugs; reassess monthly

Pharmacologic options and quality of evidence

Symptom	Commonly used options	Evidence level
Depression	SSRIs, mirtazapine, venlafaxine; ECT	Low (small trials, open-label)
Irritability	SSRIs, olanzapine, risperidone, valproate	Low (open-label, case series)
Anxiety	SSRIs/SNRIs, buspirone	Very low (extrapolated)
OCD / perseveration	SSRIs ± atypical antipsychotic	Very low (case reports)
Psychosis	Olanzapine, risperidone, quetiapine, clozapine	Low (case series, consensus)
Apathy	No proven drug; structured activity	Very low; trials mostly negative

Evidence grading is the presenter's summary of the literature; no HD-specific RCTs support most psychiatric drugs.

Non-pharmacologic and multidisciplinary care

Psychological

- CBT (adapted for cognition)
- Behavioural activation
- Supportive counselling
- Family therapy

Lifestyle

- Regular exercise
- Sleep hygiene
- Daily structure and visual schedules
- Social and day activities

Support

- Caregiver education and respite
- Social work, advance care planning
- Speech, OT, physio
- HD Society of America / EHDN resources

Medications that need care in HD

Drug / class	Concern	Mitigation
Tetrabenazine, deutetrabenazine	Boxed warning: depression and suicidality	Screen before and during; avoid in untreated depression
Valbenazine	Warning: depression/suicidality in HD	Monitor; use caution
Antipsychotics	Parkinsonism, dysphagia, sedation, metabolic	Lowest effective dose; monitor
Benzodiazepines	Falls, cognitive worsening, dependence	Short term only
Anticholinergics / TCAs	Cognitive and anticholinergic effects	Avoid where possible

Case vignette

48-year-old man, 4 years since HD diagnosis (CAG 43), on tetrabenazine for chorea. Wife reports 3 months of withdrawal, poor sleep, outbursts and loss of interest in hobbies. He says he is "fine" but recently lost his job.

Discussion

- What is the differential: apathy, depression, medication effect?
- How should suicide risk be assessed?
- What would you change in the medication list, and what first-line treatment would you consider?

Research gaps and emerging directions

- Few adequately powered RCTs for HD neuropsychiatric symptoms
- Need validated apathy and irritability outcome measures
- Trials needed: SSRIs, mirtazapine, behavioural therapy, structured interventions
- Disease-modifying approaches (e.g., huntingtin-lowering) may alter NPS trajectories
- Biomarkers (NfL, imaging) may identify risk and stage

Key takeaways

- NPS are common, early, and drive disability and caregiver burden
- Distinguish apathy from depression
- Ask about suicide at every visit, especially at transitions
- Treat the most disabling symptom; one change at a time
- Evidence is limited: combine pharmacologic and non-pharmacologic care

Questions? That’s all you had to say!”

